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EXAMINER	
FOSTER, CHRISTINE E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/652,372	Applicant(s) ADEMA, ENNO	
	Examiner Christine Foster	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 3 and 5 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4 and 6-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Please note that the Examiner in this application has changed. The new Examiner, Christine Foster, may be reached at 571-272-8786.

Applicant's amendments, filed 2/26/07, are acknowledged and have been entered. Claims 1 and 12 were amended. Claims 1-15 are pending in the application, with claims 3 and 5 currently withdrawn.

Objections/Rejections Withdrawn

1. The rejections of claims 1-2, 4, 6-7 and 11-12 under 35 USC 102(b) as being anticipated by Plattner et al. have been withdrawn in response to the amendments to claims 1 and 12.
2. The rejections of claims 8-9 under 35 USC 103(a) as being unpatentable over Plattner et al. in view of Exner et al., and of claim 10 as being unpatentable over Plattner et al. in view of Nesheim et al. have been withdrawn in response to the amendments.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Plattner et al.

Plattner et al teach measuring total AT-III activity by taking advantage of the fact that AT-III inhibits human (z-thrombin and heparin potentiates the activity of AT-III, wherein it is

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possible to delineate the inhibition of thrombin by AT-III from other plasma proteins (i.e. thrombin essentially does not interact with AT but interacts with interfering factor) by measuring a reaction mixture between thrombin and a chromogenic substrate (i.e. adding a second reagent R2; suitable for immunological determination) through measuring total AT-III as an entity (i.e. adding third reagent R3 to change the conditions such that the AT binding partner interacts with AT and conducting a second determination of free fraction of AT binding partner; R3 separate from R1) distinct from the "progressive anti-thrombin activity" measured in the absence of heparin (i.e. first determination of free fraction of AT binding partner), such that the amount of AT-III and the amount of color produced from the substrate cleavage by thrombin are inversely proportional, and the level of AT-III can therefore be readily determined (i.e. determining the AT content in the sample from the difference between the first and second determinations of the free fraction of thrombin; kinetic determination). See column 6, line 28 to column 7, line 6.

Because Plattner et al. teaches all claimed reagents for measuring antithrombin III (i.e., (a) a first reagent R1 comprising an AT binding partner (thrombin); (b) a second reagent R2 for determining the free AT binding partner (chromogenic reagents that are substrates for thrombin) and (c) a third reagent R3 (heparin)), the reference is anticipatory.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1-2, 4, 6-7, and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. (US 4,219,497) in view of Furatu (EP 0 041 366), Morris et al. (US 4,314,987), and Akhavan-Tafti et al. (US 6,068,979).

Plattner et al teach a method of measuring total AT-III activity by taking advantage of the fact that AT-III inhibits human (z-thrombin and heparin potentiates the activity of AT-III, wherein it is possible to delineate the inhibition of thrombin by AT-III from other plasma proteins (i.e. thrombin essentially does not interact with AT but interacts with interfering factor) by measuring a reaction mixture between thrombin and a chromogenic substrate (i.e. adding a second reagent R2; suitable for immunological determination) through measuring total AT-III as an entity (i.e. adding third reagent R3 to change the conditions such that the AT binding partner interacts with AT and conducting a second determination of free fraction of AT binding partner; R3 separate from R1) distinct from the "progressive anti-thrombin activity" measured in the absence of heparin (i.e. first determination of free fraction of AT binding partner), such that the amount of AT-III and the amount of color produced from the substrate cleavage by thrombin are inversely proportional, and the level of AT-III can therefore be readily determined (i.e. determining the AT content in the sample from the difference between the first and second determinations of the free fraction of thrombin; kinetic determination). See column 6, line 28 to column 7, line 6.

Thus, the reference teaches determining total AT-III activity (in which case the measurement occurs in the presence of heparin) as well as progressive anti-thrombin activity (in which case the measurement occurs in the absence of heparin). Both of these measurements are performed by detecting thrombin activity on a chromogenic substrate as instantly claimed.

Plattner et al. differs from the claimed invention in that it fails to specifically teach conducting these two measurements in a single reaction mixture. In other words, Plattner et al. teach performing the claimed determination steps *in parallel*, while the instantly claimed invention requires that they be performed *sequentially*, on the same sample or reaction mixture.

However, it was known in the art to subject a single sample to multiple measurements in sequence. For example, Furatu et al. teach subjecting a sample to a plurality of reactions sequentially (see especially pages 1-4). In one embodiment, a reagent solution containing an enzyme is added to a sample solution to cause enzyme reaction, and the result is determined by colorimetric detection (page 3, the first paragraph). Next, a second reagent solution is added to the first reagent solution and a second detection step is performed (page 3, the last paragraph to page 4, first paragraph).

Furatu et al. teach that one advantage of one advantage in performing a plurality of measurements on a single sample is that only a very small amount of a sample is used, which decreases the sampling number and omits the need for successive sampling operations (page 2).

Morris et al. teach performing a continuous sequence of tests in time on the same blood sample in order to avoid numerous errors that may be introduced by delays in time, differences in blood samples, etc. (column 3, lines 32-53).

Akhavan-Tafti et al. teach that it is frequently desirable to be able to detect and/or quantify more than one analyte at a time in a single test system; savings in time, reagents and materials can thereby be realized and assay protocols can be simplified (column 1, lines 55-63). The solution proposed by Akhavan-Tafti involves sequential detection (see especially the title and abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to detect thrombin activity in the absence and in the presence of heparin as taught by Plattner et al., but to perform these two measurements *sequentially* in the same reaction mixture rather than in parallel. Performing multiple measurements on a single sample was known in the art, as taught for example by Furatu et al., Morris et al., and Akhavan-Tafti et al. Although these references do not relate to determination of AT-III specifically, given that the chemistry of AT-III/thrombin reaction were well established at the time of the invention (as taught for example in Plattner et al.), it would have been further obvious to perform the measurement of “progressive anti-thrombin activity” in the absence of heparin first, and to then add heparin for determination of total AT-III activity. One would be motivated to perform the measurements sequentially on a single sample in order to minimize the amount of sample required, in order to save time, reagents, and materials, in order to simplify assay protocols, and in order to reduce errors due to delays in time and/or differences in blood samples.

7. Claims 8-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Exner (US 6,051,434).

The Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fail to specifically teach that the first reagent R1 comprises polybrene.

Exner teaches a mixture including polybrene, in order to reverse the effect of any heparin that may be present in test samples. See column 3, lines 34-37. It would have been obvious to

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one of ordinary skill in the art at the time of the invention to include polybrene, as taught by Exner, in the step of measuring the progressive anti-thrombin activity, as taught by Plattner et al, in order to reverse the effect of any heparin that may be present in test samples. Since the measurement step of Plattner et al requires determining the activity of anti-thrombin in the absence of heparin, the inclusion of polybrene would ensure the success of the assay, thereby providing motivation to combine Plattner et al and Exner references. In addition; one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the polybrene of Exner in the method of Plattner et al. Furatu, Morris et al., and Akhavan-Tafti et al., since Plattner et al teach measurement steps excluding thrombin:AT-III interaction, and the polybrene of Exner is well known in the art as capable of preventing the effect of heparin on inducing thrombin:AT-III complexes.

8. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Nesheim et al (US 5,308,755).

The Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fails to specifically teach an additional AT binding partner.

Nesheim et al teach the addition of purified Factor Xa, in order to perform a competition assay with heparin for antithrombin III to determine the level of heparin activity. See column 2, line 51 to column 3, line 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. with the

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addition of purified Factor Xa, as taught by Nesheim et al, in order to perform a competition assay with heparin for antithrombin III to determine the level of heparin activity. Determining the level of heparin activity, as taught by Nesheim et al, would indicate the extent of interaction heparin has with the relationship between thrombin and antithrombin III, as taught by Plattner et al, thereby providing the motivation to combine Plattner et al and Nesheim et al references. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the step of Nesheim et al in the method of Plattner et al, since both Plattner et al and Nesheim et al teach homogenous assays that include heparin and antithrombin III.

Response to Arguments

9. Applicant's arguments, filed 2/26/07, have been fully considered.
10. With respect to claims 13-15 under 35 USC 102(b) as being anticipated by Plattner et al., Applicant argues (see page 5) that Plattner et al. does not teach a kit that would include claimed reagents (a) and (c) as separate components. This is not found persuasive because Plattner et al. teaches determining both total AT-III activity as well as "progressive anti-thrombin activity", which is measured *in the absence of heparin*, which makes clear that the reagents (a) and (c) can be provided separately. Furthermore, Applicant is reminded that USPTO personnel are to give claims their broadest reasonable interpretation. In the instant case, the claims do not require that the reagents be provided in separate containers, for example, only that they are "separate". This could also be interpreted as referring simply to the requirement that the reagents be different from each other, which is also the case in Plattner et al.

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11. Applicant's arguments respect to the rejections of claims 1-2, 4, 6-7 and 11-12 under 35 USC 102(b) as being anticipated by Plattner et al. have been considered but are moot in light of the new grounds of rejection set forth above.

12. Applicant's arguments with respect to the rejections of claims 8-10 under 35 USC 103(a) as being unpatentable over Plattner et al. have been considered; however, because Applicant has not separately argued the limitations of these dependent claims, the arguments are also moot in light of the new grounds of rejection set forth above.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax

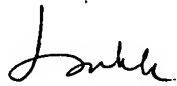
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phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Christine Foster, Ph.D.
Patent Examiner
Art Unit 1641


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